D-2-hydroxyglutarate produced by mutant IDH1 perturbs collagen maturation and basement membrane function.

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Public Summary:
Isocitrate dehydrogenase-1 (IDH1) R132 mutations occur in glioma, but their physiological significance is unknown. Here we describe the generation and characterization of brain-specific Idh1 R132H conditional knock-in (KI) mice. Idh1 mutation results in hemorrhage and perinatal lethality. Surprisingly, intracellular reactive oxygen species (ROS) are attenuated in Idh1-KI brain cells despite an apparent increase in the NADP(+)/NADPH ratio. Idh1-KI cells also show high levels of D-2-hydroxyglutarate (D2HG) that are associated with inhibited prolyl-hydroxylation of hypoxia-inducible transcription factor-1α (Hif1α) and up-regulated Hif1α target gene transcription. Intriguingly, D2HG also blocks prolyl-hydroxylation of collagen, causing a defect in collagen protein maturation. An endoplasmic reticulum (ER) stress response induced by the accumulation of immature collagens may account for the embryonic lethality of these mutants. Importantly, D2HG-mediated impairment of collagen maturation also led to basement membrane (BM) aberrations that could play a part in glioma progression. Our study presents strong in vivo evidence that the D2HG produced by the mutant Idh1 enzyme is responsible for the above effects.

Scientific Abstract:
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